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EXAMINER

MOSHER, MARY

ART UNIT PAPER NUMBER

1648

DATE MAILED: 05/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/069,056

Applicant(s)

NUESCH ET AL.

Examiner

Mary E. Mosher, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/11/02, 6/7/02, 7/29/02, 8/5/02, 3/3/02.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) 1-8, 10-16 and 18 is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) 9 and 17 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>6/7/02</u> . | 6) <input type="checkbox"/> Other: _____ |

Specification & Claims

This application is available to the examiner only as an image file wrapper (IFW). The image file wrapper for this case is more confusing than the usual, so the examiner is not sure that the correct version of the specification and claims has been examined. Please confirm if: Application papers were filed with PCT on 11 Feb 2002, the specification was 11 pages long; claims 1-13 as amended by article 34 were the claims originally presented in the US national application; there were 6 sheets of figures, with Fig. 1 (4 pages) and additional figs. 1.1, 1.2, 1.3, and 1.4. There was a preliminary amendment filed Feb. 11, 2002, which made changes to specification pages 1, 4, and 7, changes to claims 1-6 and 9-12, and added claims 14-18. A signed inventor's declaration was filed sometime in July 2002. It would be helpful if applicant could review the IFW application on PEAR and help the examiner annotate the correct document types and dates, since there appear to be many errors in the IFW indexing for this case.

In addition, regarding sequence compliance, it appears that the paper & CRF copies filed 6/20/2002 were actually processed, and the CRF filed 3/3/03 was never processed. However, it does not appear that any of the paper or CFR submissions included the required statement regarding new matter (37 CFR 1.821(g)). Still further, it does not appear that the amendments to the specification & claims refer to the correct SEQ ID numbers. Please correct the omission of the 1.821(g) statement, and review the amended application for errors.

Claim Objections

Claims 9 and 17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to other claims as alternatives only. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claims 3, 4, 6, 14-16, 18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 is drawn to an NS1 variant protein, which has (1) replication reduced, transcription eliminated, and cytotoxicity unchanged or increased, or (2) replication and transcription unchanged or increased and cytotoxicity "reduced and eliminated." Referring to Table 1, it is apparent that T363A has replication eliminated and cytotoxicity decreased, T394A has replication eliminated and cytotoxicity unchanged, T463A has replication decreased and cytotoxicity decreased. Therefore mutations T363A, T394A, and T463A are apparently excluded from claim 1, and claims 3, 4, 6, and 14 expand rather than limit the scope of parent claim 1. This affects the dependent claims.

Claim Rejections - 35 USC § 112

Claims 1-8, 10-16, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, what is meant by "activity (b) is reduced and eliminated, respectively"? Activity (b) is "cytotoxicity", how can it be both reduced and eliminated, and what does "respectively" refer to? Furthermore, it is not clear what applicant means by

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“transcription activity”; this is only defined by an improper incorporation by reference to a publication.

Parent claim 1 refers to a generic parvovirus NS1 protein, and claim 3 refers to specific residues 283, 363, 394, 463. Since the length of NS1 can vary in different parvoviruses, is the intent really to specify these particular positions in any NS1 regardless of whether or not they function in the same way as these positions in SEQ ID NO: 2?

Claim 4 is confusing. First, it is drawn to an NS1 Protein but refers to SEQ IDs 4 and 8, which are DNA sequences. Second, the mutation at residue 363 is not present in SEQ ID NO: 6, and the mutation in residue 463 is not present in SEQ ID NO: 10. Third, is the intent to require the specifically recited NS1 sequence, or to require a mutation at the recited site? These are different in scope. This problem also affects claim 14. In addition, in claim 14, is the intent to require mutation at the recited sites, or to require specific amino acids at the recited sites, or to require one protein to include all four of the recited SEQ IDs?

In claim 6, SEQ IDS 3, 5, and 9 are amino acid sequences, not DNAs, and SEQ 7 is an incomplete NS1 sequence. In part (a), is the intended scope the specifically recited DNA or a DNA with a mutated phosphorylation site, and is the phosphorylation site in the DNA or in the protein encoded by the DNA? Is part (b) meant to encompass oligonucleotides that hybridize to nonmutated parts of DNA (a)? And if part (b) includes some variation from a disclosed sequence, how is one to determine whether or not any

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oligonucleotide of part (c) is related "via the degenerated genetic code" to the undefined changes permitted in part (b)?

Claim 8 is drawn to "a transformant containing the expression vector according to claim 7." Since applicant intends to use the expression vector for gene therapy and treating tumors, is the intent really to claim ownership of humans undergoing therapy?

In claim 11, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention.

See MPEP § 2173.05(d).

Claims 12-13 provide for the use of the protein of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

In claims 10 and 18, it is not clear if the claimed antibody includes antibodies which react both with the mutant NS1 and with nonmutated NS1. Therefore the scope of the claimed antibodies is indefinite.

These problems affect the dependent claims.

Claims 1-8, 10-16, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for NS1 variants S283A, T363A, T394A, and T463A, does not reasonably provide enablement for "a shifted equilibrium between the DNA replication and transcription activities (a) and the cytotoxicity activity (b), or even for the Markush group recited in claim 1. The specification does not enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 1 is drawn to an NS1 variant protein, which has (1) replication reduced, transcription eliminated, and cytotoxicity unchanged or increased, or (2) replication and transcription unchanged or increased and cytotoxicity "reduced and eliminated." Table 1 is supposed to illustrate these activities, but there is no explanation of how the cryptic labels relate to replication, transcription, and toxicity. At a guess, "Rep" refers to some measure of replication, and "Cyto" refers to some measure of toxicity. If this is correct, then it is apparent that mutant S283A has replication reduced and cytotoxicity increased, T363A has replication eliminated and cytotoxicity decreased, T394A has replication eliminated and cytotoxicity unchanged, T463A has replication decreased and cytotoxicity decreased. Therefore mutations T363A, T394A, and T463A are excluded from the Markush group recited in claim 1. Consequently, the only guidance the specification provides to achieving any of the functions recited in the claim is to mutate position 283 in whatever species of NS1 was used for the working examples.

Furthermore, there does not appear to be any "equilibrium" between cytotoxicity and replication activity, because two mutations decrease both activities, one mutation affects one activity without affecting the other, and one mutation has opposite effects on the two activities. Because the specification does not provide any evidence that there is an "equilibrium" as recited in the claims, nor teach where to mutate the NS1 protein to achieve the full scope of results recited in the claims, it is concluded that undue experimentation would be required to enable the full scope of the invention as claimed.

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Claims 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 12-13 involve "treating tumoral diseases" and "gene therapy". The specification provides unsupported assertions that the disclosed products would be useful for these therapies, but provides no guidance and no working examples of these uses. A review of the prior art does not indicate that use of parvovirus NS1 proteins for tumor therapy or in gene therapy vectors is routinely practiced in the art. Considering the quantity of experimentation involved in developing a new therapy, the limited disclosure in the specification, the absence of working examples, and the art-recognized difficulties in treating tumors and in successfully practicing gene therapy, it is concluded that undue experimentation would be required to practice these claims.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cultured cells containing an expression vector, does not reasonably provide enablement for the full scope of "transformant" claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification teaches how to use expression vectors in cultured cells, but does not teach how to make a stably transformed animal comprising an expression vector, or how to use the stably transformed animal. Furthermore, since many of the disclosed expression vectors exist only transiently in intact animals (and

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humans), this means that applicant would own the host while the vector is present and lose ownership once the vector is eliminated. The specification does not teach how to determine when this change in ownership occurs. Therefore it is concluded that undue experimentation would be required to make and use the full scope of "transformants" claimed.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 8, 12, and 13 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 8 encompasses a human being (e.g. a person undergoing therapy). Claim 8 is rejected because human beings are not patentable subject matter. Claims 12-13 are rejected because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-8, 11, 14, 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Legender et al (Journal of Virology 66:5705-5713, 1992, cited in IDS). See Figure 1. The NS1 mutant pULB3201 has DNA replication activity reduced (to undetectable), p38 transactivation eliminated, and cytotoxic activity maintained. This deletion mutant includes the sites recited in claims 3 and 14. Therefore the publication meets each and every limitation of these claims.

Claims 10 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Yeung et al (Virology 181:35-45, 1991). Yeung teaches antibodies directed against portions of the NS1 protein of MVM. Since these portions are found in NS1 proteins encompassed by claims 1 and 4, the antibodies are inherently directed against proteins of claims 1 and 4. The reference therefore meets each and every limitation of these claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 10, 11, 14, 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Moffatt et al (Journal of Virology 72:3018-3028, April 1998). Moffatt teaches a mutated B19 NS1 protein which has reduced cytotoxicity and maintained trans-activation of transcription of an IL6 promoter. One of these mutations changes a threonine residue, which reasonably appears to be a phosphorylation site (since three of the four sites disclosed by the instant specification involve mutation of a threonine residue). Moffatt also teaches an antibody reactive with the NS1 protein. The reference is silent upon the replication activity of the mutant protein, and the Patent Office does not have the facilities to manufacture and test the Moffatt protein for this activity. However, the Moffatt protein appears to be substantially identical to the claimed NS1 protein. See In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) [PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical.]

Conclusion


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is 571-272-0906. The examiner can normally be reached on M-T and alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

5/26/04


MARY E. MOSHER
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